Editorial

Developing Confidence in Risk Assessments Based on Physiological Toxicokinetic Models

A physiologically based toxicokinetic model typically represents the uptake of a toxicant by a laboratory animal, its distribution to various organs, its metabolic activation and/or detoxication, and elimination of the parent compound and its metabolites. The aim is to predict the dose response of the actual toxic agent (parent compound or metabolite) in the tissue that ultimately develops symptoms of toxicity. In many cases, a subsequent response stimulated by the toxic agent may be mechanistically related to the ultimate health outcome and can serve as an indicator of the effects of the administered chemical. A model can quantify this response as a function of dose, permitting it to be used as a dose surrogate in estimating the toxicant's effects at low exposures. Because toxicokinetic modeling incorporates a large amount of information about the animal beyond the observation of the incidence of the endpoint at various doses, it offers a method of reducing the uncertainties in risk assessments based solely on external exposure.

Although human physiology is qualitatively similar to that of laboratory animals, the rates of some of the physiological and biochemical processes, and hence tissue dosimetry, differ quantitatively among species. Two of the most difficult but critical problems in risk assessment are identifying doses to humans that are equivalent to doses given to laboratory animals and predicting the shape of the dose–response curve at doses too low to yield a response that can be distinguished from interindividual variability. If experimentally determined parameter values for humans are available to replace the corresponding values for a laboratory animal in a validated dosimetric model, then the model could be used to predict tissue dosimetry in humans. Including human interindividual variability in the model could permit identification of susceptible subpopulations. A mathematical model based on physiological principles incorporates mechanisms thought to relate dosimetry to toxicity, and it provides a stronger scientific foundation for estimating equivalent doses across species, including humans, than does the default method of allometric scaling.

In order to develop confidence in biologically based risk assessments, a model must provide a realistic representation of the biological system and describe the relationship between exposure to a chemical and responses leading to its toxic effects. For example, in a realistic model of inhalation of a gas from an enclosed chamber, inhaled material passes through the alveolar space and lung capillary blood before mixing with the general circulation. Simple models in which gas in the chamber equilibrates directly with the entire blood volume produce an artificial dilu-

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tion effect on dissolution of the gas in blood, leading to larger concentration gradients between inhaled air and blood and consequently more rapid calculated gas uptake. Similarly, inclusion of tissue capillary spaces in the model leads to smaller blood:tissue gradients than do models which do not include this representation of blood distribution. A realistic model would predict greater activity of a metabolizing enzyme in order to reproduce a given clearance rate than would a model in which toxicant in the metabolizing tissue equilibrates with the entire circulation. Simplified models that consider all metabolism of the toxicant to occur in the liver even though the metabolizing enzyme is also known to be expressed in other tissues may reproduce the observed uptake of the toxicant because of the overestimation of the rate of distribution via the blood. Because the computed dosimetry is sensitive to the mathematical description of lung and blood physiology, predictions based on a realistic representation of anatomy would be expected to more closely reflect the true biological behavior. Measurements of enzymatic activity and metabolite concentrations in various tissues could resolve this ambiguity.

Toxicokinetic models can exhibit a curious combination of sensitivity to the values of physiological and biochemical parameters and a lack of robustness. Measurements of partition coefficients from different laboratories frequently differ by factors of 2–4; measured activities of metabolizing enzymes in a given tissue may vary by an order of magnitude. Significant differences in the fit of a model to experimental data for uptake and clearance often can be obtained by using different particular measured values for one parameter while keeping other parameter values fixed. However, there is usually a sufficient number of adjustable parameters in a model to permit an adequate fit to limited data on the biological fate of the toxicant. Parameter values obtained by fitting uptake data by formal optimization can vary considerably depending on which measured value is included in the model. This lack of robustness arises from the nonidentifiability of the parameters owing to such a limited data set and could be avoided if time–course data for blood and tissue concentrations of parent compound and/or metabolite(s) were available. Ideally, time courses of metabolic intermediates should be obtained for the same experiments that provided the uptake and elimination data.

Validation of models requires that the model reproduce data other than those used to estimate the model's parameters; otherwise, the modeling procedure is merely an exercise in curve fitting. For example, toxicokinetic models with differing levels of detail
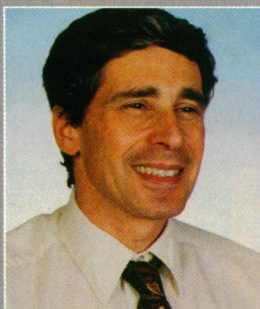
can give comparable fits to uptake data but make different predictions for concentrations of intermediates and metabolic cofactors. Most models in which a toxicant is cleared by conjugation with a cofactor describe this enzyme by hyperbolic kinetics with respect to the substrate but neglect both the binding of the cofactor and its depletion by the chemical reaction. If parameters in such a simplified model are estimated to reproduce only the rate of uptake of the chemical, the model may fail to reproduce the effect of the chemical on cofactor concentration. Therefore, confirming that a model fits data sets for different measures other than those used in its construction permits discrimination among competing models.

There is a long sequence of biological events between delivery of a toxicant to target tissues and the production of the ultimate adverse health effect. These events might include mutagenicity consequent to formation and misrepair of adducts with DNA bases or altered expression of mitogenic proteins induced by a complex between the toxicant and a transcription factor. Toxicokinetic models almost never are extended to include such events, thus leaving a gap between tissue dosimetry and the ultimate response. Measurement of such responses, for example, accumulation of DNA adducts or production of induced proteins, are necessary to extend toxicokinetic models beyond dosimetry and identify quantitative relationships between tissue dose of a toxicant and those biomarkers. More realistic biologically based models would improve estimates of site-specific human dose responses associated with risk of adverse health effects.

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CAAT Recognition Award

The Johns Hopkins Center for Alternatives to Animal Testing (CAAT) would like to honor and individual or organization who has made an outstanding contribution to the field of 3Rs alternatives and in vitro sciences. We invite the readers of this journal to submit nominations. The award will be presented at the second World Congress on Alternatives and Animal Use in the Life Sciences, to be held in October 1996 in Utrecht, The Netherlands. Deadline for receipt of nominations is June 1, 1996. Please send your nomination, including a one-page description of why this individual or organization should be recognized. Please include a curriculum vitae for individual nominees and a fact sheet or supporting documents for organizations. A subcommittee of the CAAT Advisory board will review the nominations and select the recipient of the CAAT Recognition Award

Forward nominations to: Alan M. Goldberg, Ph.D., Johns Hopkins Center for Alternatives to Animal Testing 111 Market Place, Suite 840, Baltimore, MD 21202-6709